Testimony Made to the Food Advisory Committee Meeting on Infant Formula on April 4, 2002 and Further Comment:

My name is Susan Carlson and I am a Professor of Dietetics and Nutrition and Pediatrics at the University of Kansas Medical Center in Kansas City, KS. I am speaking to you today from the perspective of experience gained as the PI on five clinical studies conducted at the University of Tennessee, Memphis, while I was in the professorial rank at the University of Tennessee, Memphis in Pediatrics, Ob-Gyn and Biochemistry.
The clinical trials involved feeding ordinary formula compared to an experimental formula differing only in the addition of LCPUFA, either docosahexaenoic acid (DHA) or arachidonic acid (ARA) to preterm or term infants. The three preterm trials that we conducted were funded jointly by the NICHD and Ross Laboratories. One of the term trials was funded by Ross Laboratories and one was funded by Mead Johnson. The latter was a multi-center trial on which I was the senior investigator outside of Mead Johnson. I am present today as a paid consultant of Wyeth Ayerst, but I have never done a clinical study supported by Wyeth Ayerst. The opinions I present to you today are my own.

In two of the trials involving very preterm infants (<1500 g birth weight), infants fed DHA from a fish oil source had somewhat lower growth than infants fed the formula without DHA (1,2). I have analyzed these trials on several occasions (3-5), most recently a review with Alexandre Lapillone at the Childrens' Nutrition Research Center in Houston (5). To briefly summarize my view, which is supported by data collected by ourselves and others, infants who benefit from dietary DHA may also need ARA, because the enzymes for synthesis are identical through the delta-5 desaturase step that forms ARA and eicosapentaenoic acid (EPA). Partly as a result of my published comments (2,3), experimental formulas with ARA and DHA were developed. The combination of ARA and DHA in an experimental formula has not shown any effect on growth in comparison to formulas without ARA and DHA in any subsequent study of preterm infants, in support of the our earlier speculation in PNAS (3). I want to return to the growth assessment of term and preterm infants at the end of my comments. . I believe that I have spent as much time examining the growth of formula-fed infants as anyone in the field of pediatric nutrition, and that I have examined the growth of as many infants without organic growth problems as any other person.

When is it appropriate to generalize the results from clinical studies done in one population to another population, whether the difference in populations be cultural, geographic, gender, age, physiologic maturity, etc? This is the question posed by the FDA to the committee, which I want to address today using the specific example of normal physical growth

As the specific questions put by the FDA center on decisions they need to make regarding infant formula, I will also restrict my comments to the complex matrix of different ingredients that supply nutrients essential for optimal growth and development when fed as a sole source of food to infants.

As much as possible, investigators seek to design studies that can be generalized beyond the population they are studying, but the ability to generalize data is never completely possible from any single-population study, however large. Even seemingly identical studies carried

out several years apart may yield a different outcome, i.e., information gained from the first study may not be generalized to the second. In part, because scientists understand that uncontrolled factors, both known and unknown, may influence the study outcomes, the scientific community expects that an intervention will be tested in a variety of populations before conclusions about a finding can be accepted. Studying an intervention in different populations in most cases actually strengthen the conclusions that can be drawn, and I maintain that this is the case for the studies of DHA and DHA plus ARA vis-à-vis growth. These have now been done in a number of different geographical locations, in populations of infants whose mothers have different cultural patterns of food intake and bear their children at different ages, in infants born early in the 3rd trimester of gestation and infants born at term, and with DHA and ARA from different sources [egg phospholipids and triglycerides, fish oils (low and high EPA), and single cell oils]. Because of this (not despite this), it may be concluded that DHA and ARA together are unlikely to adversely influence growth of either preterm or term infants.

On the specific question of whether data generated in preterm infants can be generalized to term infants or visa versa, and considering the issue of normal physical growth, the answer is "It depends." I propose to give an example for growth in infants fed DHA or DHA and ARA. VLBW infants quadruple their weight between birth at 28 weeks gestation and 2 months corrected age. Term infants only triple their weight between birth at 40 weeks and 12 months of age. Clearly, a formula or an ingredient in formula that does not affect growth of preterm infants compared to growth of preterm infants fed an accepted formula or formula without that ingredient should not pose any particular concern for growth of term infants. On the other hand, the reverse might not be the case, since growth of the term infants is statistically speaking much less sensitive an indicator than that of preterm infants.

Dr. Lapillone and I reviewed the growth of term and preterm infants fed experimental formulas with either DHA or DHA and ARA (5). From the summary review, I made clear assumptions about those with the power to conclude "no effect" on growth using the attached slides. Only studies with adequate power to reach the conclusion of no effect should be kept in evidence as concluding "no effect" in error means that some infants could be put at risk for lower growth due to that intervention. To summarize the message of these slides, preterm infants but not term infants have been shown to have lower growth when fed formula with DHA compared to a commercial formula without DHA. Preterm infants fed DHA and ARA have not been shown to have lower growth compared to a commercially available formula. From the above, I conclude that data from preterm infants fed DHA and ARA can be generalized to term infants for the purpose of growth as an outcome. On the other hand, as in the example given in the slides, one may not generalize data from term studies to studies of healthy preterm infants, because term infants fed DHA without ARA did not show lower growth but preterm infants did. [It follows, that one may not generalize from term infant to sick preterm infants on this issue. This seems an obvious point, but took up an extraordinary amount of discussion time at the hearing.]

I would like to add two new comments that were stimulated by the question and answer period and committee discussion that followed.

My first comment is related to the issue of formula matrix. As I see it, the matrix of a formula is important for two main reasons. First, the source of ingredients may influence bioavailability. Much is known about this by the industry, and the committee itself contains a great deal of expertise for addressing concerns in this arena. I have no expertise in this area. Second, the potential for interaction of nutrients themselves inevitably influences bioavailability. In this arena I and other nutritionists feel quite comfortable. We have a good understanding of how these interactions occur and which ones are functionally relevant. Most important, nutritionists understand that it is possible to prevent these interactions from becoming functionally important. For example, in order not to decrease the amount of a nutrient that is bioavailable below what is required, nutrients are provided in amounts comfortably in excess of the minimum and well below the amount that could be toxic Another important point, which I did not hear made, was that with regard to a new ingredient, there is no example where the addition of a new ingredient has increased bioavailability of any nutrient already in infant formula from the range of safe to the range of toxic. Therefore, concerns about a new ingredient adversely influencing growth due to a nutrient toxicity is a "nonissue" when it comes to the addition of a new ingredient to a formula mixture that supports normal growth.

The discussion in the early afternoon of the 4th of April was centered on principles from the COMA summary. It was not clear to me why these were discussed in such detail and I was unable to attend the remainder of the session. Perhaps the rationale would have become clear to me. I do believe the COMA is relevant to inform the discussion of what kinds of trials have the most validity when it comes to generalizing data from one population to another. I would not have assumed from the make-up of the committee that such as discussion was needed, however. Of course, it is important to take into account the quality of the data when determining if a study can be generalized to another. As I tried to point out in my earlier comments, in the real world, one never gets the perfect study for consideration. Given that, one must make decisions with a variety of studies that together add up to more than a single study. I believe that this process of moving forward creates the most safety for implementation of an intervention and minimizes the very real risk of denying populations the benefit of receiving worthwhile interventions in a timely manner.

I would be pleased to answer any questions that might be generated by this letter and can be reached as indicated below.

Sincerely yours,

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